Chemistry of Natural Compounds, Vol. 49, No. 3, July, 2013 [Russian original No. 3, May–June, 2013]

BRIEF COMMUNICATIONS

SYNTHESIS OF A BISPHOSPHONATE DERIVATIVE OF FOLIC ACID

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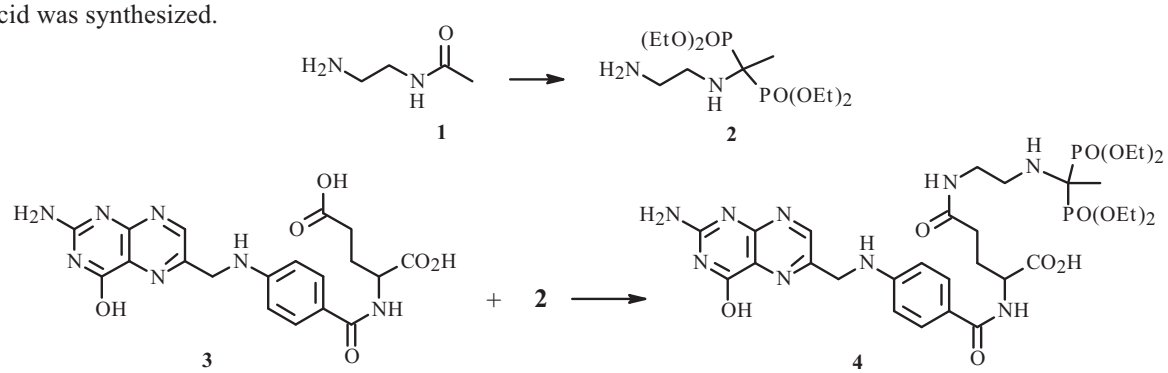
UDC 547.859.1

1-Amino-1,1-bisphosphonates are attracting heightened attention in various sectors of chemistry and medicine owing to a combination of unique chemical, physical, and biological properties. The combination of these properties opens possibilities for molecular design and synthesis of various biologically active compounds that are used as immunomodulators, calcium-exchange regulators, and antitumor drugs [1]. Complex conjugates of bisphosphonates and natural biologically active compounds have recently become interesting. Thus, bisphosphonates based on widely known antibiotics of the fluoroquinolone series [2] and the folic-acid antagonist methotrexate, which is used to treat neoplastic diseases [3], were synthesized. Targeted delivery of drugs through covalent binding of carboxymethylchitosan nanoparticles and folic acid was recently found to be possible. It was assumed that the latter would assist penetration of the nanoparticle into the cell and cause its apoptosis [4].

The present communication reports the synthesis of the conjugate of a bisphosphonate derivative and folic acid. A one-step synthesis using the structural synthetic building block 1-(2-aminoethylamino)-1-(diethylphosphoryl)ethylphosphonic acid diethyl ester (**2**) was proposed for modifying folic acid. Compound **2** was obtained in 45% yield by phosphorylation of *N*-(2-aminoethyl)acetamide (**1**) (2.2 g, 22 mmol) by analogy with the literature method [5]. The reaction of folic acid (**3**) (0.20 g, 0.45 mmol) and **2** (0.19 g, 0.53 mmol) in the presence of dicyclohexylcarbodiimide (0.28 g, 1.36 mmol) was carried out according to the literature method [4]. The yield of 2-{4-[(2-amino-4-hydroxypteridin-6-ylmethyl)-amino]-benzamido}-5-{2-[1,1-bis-(diethylphosphoryl)-ethylamino]-ethylamino}-5-oxopentanoic acid (**4**) was 20%. The structure of the product was confirmed using PMR and ^{31}P NMR spectroscopy and mass spectrometry. Thus, the first bisphosphonate derivative of folic acid was synthesized.



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